

Research progress of novel therapeutic strategies for oral cancer

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Abstract: The incidence of head and neck squamous cell carcinoma is increasing year by year. Oral cancer, the most common subtype of head and neck squamous cell carcinoma, is initially diagnosed as locally advanced and prone to recurrence and metastasis. Although traditional surgery, radiotherapy, and chemotherapy are the first-line options, they are easy to damage the oral chewing, language function, and facial appearance and also have a series of side effects. The 5-year survival rate of patients has been long stagnating, and the quality of life is greatly reduced after surgery. In recent years, many innovative therapies have been developed for oral cancer, including heparin derivatives, molecular targeted therapy, photodynamic therapy (PDT), and photothermal therapy (PTT), which not only improve the cure rate of oral cancer but also reduce the incidence of complications. Based on the existing in vivo, in vitro, and clinical research data, these four new therapies can inhibit the occurrence and development of oral cancer alone or in combination with traditional therapies. This article reviews the clinical research and treatment progress of these four new therapies.

Keywords: oral cancer; photodynamic therapy; photothermal therapy; Non-Anticoagulant Heparin

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) ranks as the sixth most prevalent type. Globally, malignant tumors resulted in 890,000 new cases and 450,000 deaths in 2018 ^[1]. The occurrence rate of head and neck squamous cell carcinoma is steadily increasing and is predicted to increase by 30%, or 1.08 million new cases per year, by 2030 ^[2]. Oral cancer is the most common malignant tumor in head and neck cancer. According to global cancer statistics, approximately 380 000 new cases and 180 000 fatalities due to oral cancer occur, constituting 2% of the global cancer-related death toll. A number of epidemiological investigations have confirmed that HNSCC is the result of the cooperation of multiple risk factors. Long-term alcohol intake, chewing betel nut, environmental pollution, and viral infections such as human papillomavirus (HPV) and Epstein-Barr virus (EBV) can greatly increase the risk of disease ^[3-5]. The survival rate and prognosis of oral cancer are relatively poor due to multiple pathogenic factors. At the moment of first diagnosis, 60% of the patients are in a state of local progression, 15%-50% of patients may have recurrence, and 15-40% of patients have distant metastasis ^[6]. The oral and maxillofacial region is responsible for the physiological functions of speech, chewing, breathing and appearance. There are challenges in the treatment of oral and maxillofacial region: how to maximize the preservation of organ function on the basis of complete removal of tumors ^[7]. Currently, surgical procedure remain the primary therapeutic approach, supplemented by radiotherapy or chemotherapy ^[8]. Nonetheless, there are some limitations associated with these treatment. For instance, facial abnormalities caused by surgical treatment; Radiotherapy can also lead to Sjogren's syndrome, osteoradionecrosis and oral mucositis^[9]. Chemotherapy relies on elevated levels of cytotoxic drugs, known to easily trigger systemic toxicity, bone marrow suppression, and resistance to multiple drugs^[10]. Even with the latest progress in treatment techniques, the 5-year survival rate of patients with oral squamous cell carcinoma is only about 60%, and about one third of patients will experience tumor recurrence ^[11]. Considering the quality of life after surgery, the vast majority of patients are more likely to experience functional disabilities, and relevant statistics show that 73.9% of those who recover exhibit varying levels of dysphagia ^[12]. This dilemma has prompted the exploration of various novel therapeutic strategies, including heparin derivatives ^[13], Molecular targeted therapy^[14], photodynamic therapy (PDT)^[15], and photothermal therapy (PTT) ^[16]. This article reviews previously mentioned novel therapeutic approaches.

2. Novel Therapeutic Approaches

2.1 Non-Anticoagulant Heparin

Oral squamous cell carcinoma (OSCC) is the most frequent tumor among oral cancer. It poses a significant global oral health concern. Some researchers have proposed that anticoagulants can inhibit the pathways of cancer cells, and it has been confirmed that such drugs can inhibit the proliferation, migration and invasion of tumor cells^[17]. For example, the University of Melbourne developed its own Non-anticoagulant heparin(NH), a heparin derivative, serves as an encouraging approach, given the improved survival noted with anticoagulants in cancer therapies^[13].

Hamza et al.^[18] identified non-Anticoagulant Heparin as a novel strategy for oral cancer. the study selected H400, H357 OSCC cells and OKF6 normal oral keratinocytes, administering them with unfractionated heparin (UFH) and non-anticoagulant heparin (NH) in concentrations ranging from 10 to 80 μ g/mL. The MTS cell proliferation assay and cytotoxicity assay were conducted. An assessment was performed on the impact of non-anticoagulant heparin and heparin on three different oral cell lines in vitro, along with a deeper exploration of how NH and 5FU and cisplatin (1-5 μ g/mL) interact. The findings indicated that 80 μ g/mL of non-anticoagulant heparin(NH) could generate significant cytotoxic effect on both tumor cell lines, with its suppression of tumor cell proliferation at 48 h and 72 h was similar to that of heparin. The above-mentioned pair of medications are not cytotoxic to normal cells. Both heparin and NH hindered the migration and invasion of H400 and H357 cells. Crucially, the combination of cisplatin and 5-FU with primary oral chemotherapeutic drugs did not cancel the anti-tumor activities of cisplatin and 5-FU. Furthermore, the findings from Camacho and colleagues^[19] demonstrated that heparin similarly inhibited cell growth and curtailed the movement of cells in oral cancer cell lines. Ling et al.^[20] applied unfractionated heparin to the H400 cell line, and also observed the impact of hindering cell growth and movement. However, the results of proliferation assay in H357 cell line were slightly different. Consequently, this novel heparin derivative shows potential for many applications. NH, a heparin derivative, could be influential in addressing oral cancer in vitro. Non-anticoagulant heparin can inhibit proliferation, migration and invasion of tumor cells. At present, there is a scarcity of literature available for review in this field. It is still necessary to further explore non-anticoagulant heparin, refine the treatment approach and the combined medication strategy of oral cancer, and lay the foundation for clinical diagnosis and therapy.

2.2 Photothermal Therapy

Photothermal therapy (PTT), a novel treatment technique, employs photothermal reagents (PTAs) to convert near-infrared light (NIR) into localized hyperthermia, targeting heat-sensitive tumor cells and protecting healthy tissues^[21]. This treatment offers benefits such as being noninvasive, precise in both space and time, synergistic, and reusable with other treatments^[22,23]. In addition to direct tumor ablation, the heat generated by photothermal therapy (PTT) can also facilitate drug delivery, triggers the release of immunogenic antigens, reshape the tumor microenvironment (TME), and fosters bone and soft tissue regeneration, which are important to repair maxillofacial anomalies post-tumor removal^[24,25]. Zeng et al. investigated the use of nanomaterial-assisted photothermal combined chemotherapy in treating oral squamous cell carcinoma, noted for its strong biocompatibility, minimal cytotoxicity, ideal drug loading capacity, and potent photoacoustic imaging (PAI) signal. The results indicated that the nanosystem achieved an excellent photothermal conversion rate of 49.02% following treatment with PTT. experiments in vivo and in vitro verified superiority of a combined chemo-photothermal approach over individual chemotherapy or photothermal methods ($P < 0.05$). By administering DOX AuNRs@mSiO₂ HA nanoparticles injected into CAL 27 tumor-bearing mice, this material can actively prevent tumor lesion build-up; Combined with near-infrared laser irradiation, it allows for total tumor tissue removal without obvious damage to the surrounding healthy tissues. PTT can be used not only in combination with chemotherapy but also when used alongside radiotherapy for treating oral cancer. Radiotherapy (RT) uses intense ionizing radiation to eliminate residual tumor lesions, destroy tumor cells, and prevent tumor recurrence^[26]. Nonetheless, radiotherapy is primarily sensitive to G2/M phase tumor cells while exerting minimal impact S phase cancer cells^[27]. Hypoxia with tumors may additionally weaken the efficacy of radiotherapy and plays a crucial role in the tumor recurrence as well as spread of tumors post-radiotherapy^[28]. At the same time, an extensive array of ionizing radiation may affect the adjacent healthy tissues, leading to significant complications^[29]. PTT is able to enhance blood circulation locally by heating up, bettering tumor tissue oxygen levels, alleviating resistance effectively to hypoxia-mediated radiotherapy, and amplifying the effect of radiotherapy. As an illustration, Neshastehriz et al.^[30]

developed folate-coupled gold nanoparticles (F-AuNPs) that were specifically concentrated at tumor sites with the help of folate receptor-mediated targeting. Laser exposure at a wavelength of 532 nm, F-AuNPs can generate substantial tumor thermal ablation effect via local photothermal transformation. Concurrently, its elevated sub-number property (the fundamental aspect of radiosensitization) can improve the radiotherapy effect in X-ray applications. Post-treatment of tumor cells with F-aunPs, the inhibition effect of laser combined with X-ray dual irradiation on cell viability significantly surpassed that of solely photothermal therapy or radiotherapy alone. This remarkable synergistic effect indicates that the combined radiotherapy-photothermal strategy mediated by gold nanoparticles has the potential to achieve precise tumor removal while safeguarding normal tissues. Therefore, PTT, as a innovative treatment strategy, can markedly improve the effectiveness of radiotherapy and chemotherapy for oral cancer, which is more conducive to clinical treatment and boost the survival rate of patients with oral cancer.

2.3 Molecular Targeting Treatment

In recent years, the field of malignant tumor biotherapy has seen molecular targeted therapy emerge as its primary and innovative strategy. This treatment strategy focuses on the abnormally high expression of specific markers in tumor cells, and employs specific blockers to accurately intervene the crucial signal transduction pathways related to tumor occurrence, growth and metastasis, accurately block the growth and penetration of cancer cells, and then achieve the treatment purpose of curbing tumor expansion and blocking distant metastasis [31].

As an example, Su et al.[32] researched a novel targeted drug FLLL32, a man-made version of curcumin known for its anti-tumor properties; This substance is recognized for inducing apoptosis in melanoma cells and is capable of inhibiting the growth of a variety of tumors. Investigating if FLLL32 can trigger the apoptosis process in oral cancer cells. Findings showed that FLLL32 could effectively inhibit the viability of oral cancer cells. Cell cycle assay revealed a notable rise in the percentage of cells in the G2/M phase, inducing cell cycle arrest. In addition, Annexin V/PI double staining further confirmed that FLLL32 could induce apoptosis in oral cancer cells. Human apoptosis protein chip analysis revealed that FLLL32 could up-regulate the protein expression levels of activated caspase-3 and heme oxygenase-1 (HO-1). In the study of apoptosis-related molecules, FLLL32 can activate core apoptosis markers such as caspase-3, caspase-8, caspase-9, PARP, and regulate the expression and activation state of mitogen-activated protein kinase (MAPK). Furthermore, the principal signaling routes of p38MAPK-induced apoptosis in oral cancer cells were further verified by MAPK specific inhibitor DARE assay. Collectively, these results reveal that FLLL32 can activate the p38 signaling pathway to initiate apoptosis reliant on caspase and HO-1 expression, suggesting that FLLL32 has a promising treatment for oral cancer.

Moreover, Hmedat et al.[33] examined the synergistic impact of dasatinib as well as glucocorticoids in treating tongue squamous cell carcinoma. Tyrosine phosphoprotein profiling was performed on 34 tongue squamous cell carcinoma (TSCC) cell lines. It was discovered that the expression pattern of phosphorylated proteins across various cell lines were highly consistent, and all of them had a characteristic 130 kDa tyrosine phosphoprotein. Following the suppression of Src family kinase (SFK) activity, there was a remarkable decrease in the overall tyrosine phosphorylation level in tumor cells, along with a substantial reduction in the tyrosine phosphorylation of p130Cas as downstream. Experiments in vitro confirmed that SFK inactivation could effectively inhibit the proliferation of TSCC cells. The results of high-throughput combination drug screening based on dasatinib showed that glucocorticoids could play a synergistic anti-tumor effect with dasatinib. This experiment confirmed that dasatinib combined with dexamethasone could effectively inhibit the phosphorylation of Src and p130Cas and down-regulate the protein expression of p130Cas. At the same time, dexamethasone can block the phosphorylation of MET kinase and its substrate Gab1 and inhibit the malignant progression of tumors through multiple pathways. On a cellular scale, the integrated treatment could induce G1 phase cell cycle arrest, encourage cell senescence, stimulate autophagy, regulate the expression of core cell cycle molecules such as cyclin-dependent kinases (CDKs) and cyclins, and ultimately markedly reduce the malignant proliferation of tongue squamous cell carcinoma cells. The results of this study can provide new experimental basis and research ideas for optimizing and transforming tumor combined therapy clinically.

2.4 Photodynamic Therapy

Photodynamic therapy (PDT) is a new type of tumor intervention technology that has been rapidly

developed in recent years. In this protocol, photosensitive agents are infused into the body through the drug administration route, which can selectively enrich in malignant lesions. Subsequently, a specific band light source was used to locally irradiate the lesion area to activate the enriched photosensitive molecules and trigger the photochemical cascade reaction^[34]. The mechanism can hit the tumor on several occasions: on the one hand, it can directly destroy the internal organelle structure of the tumor, leading to the apoptosis and necrosis of cancer cells; On the other hand, the microcirculation of the lesion is destroyed, and the anti-tumor immune response is activated at the same time to achieve the elimination of tumor cells through multi-pathway cooperation^[35]. Pinto et al. ^[36] used 5-aminolevulinic acid (5-ALA) as a photosensitizer to conduct a photodynamic therapy (PDT) intervention experiment to explore the regulatory effect of this therapy on the biological behavior of OSCC. The effects on the phenotype and stemness of cancer stem cells (CSCs) were analyzed. Two OSCC lines were selected and divided into blank control group, 5-ALA treatment group, 6 J/cm² LED treatment group and 5-ALA-PDT combined treatment group. 5-ALA-PDT could significantly reduce the growth and movement of OSCC cells. CD44^{high}/ESA^{high} cells are more sensitive to PDT due to the enrichment of protoporphyrin IX. After PDT treatment, the proportion of this subset decreases, the ability of cell cloning and sphere formation is significantly weakened, and the expression of differentiation marker INV gene is up-regulated. In summary, 5-ALA-mediated photodynamic therapy reduced the proportion of oral cancer stem cells, inhibited their stemness and induced their differentiation. Narahara et al. ^[34] explored the long-term clinical efficacy of photodynamic therapy for OSCC and epithelial dysplasia. This clinical study saw the enrollment of 23 patients in total. At 4-week follow-up after photodynamic therapy, of the patients, 19 experienced a full response (CR, 82.6%), while the remaining 4 showed a partial response (PR, 17.4%). The long-term follow-up results showed that 11 of the 19 patients with complete remission had locoregional tumor recurrence, the recurrence rate was 57.9%, and the average recurrence time was 27.4±30.4 months. For patients with local recurrence and partial remission, surgical resection was performed, and 3 patients died of primary tumor progression. Although photodynamic therapy can achieve good lesion control effect in the short term, the long-term anti-tumor effect of this regimen is still insufficient, and a large number of studies and experiments are needed to optimize it.

A comprehensive review of the existing literature reveals that the four novel intervention strategies summarized in this paper—non-anticoagulant heparin, photothermal therapy, molecularly targeted therapy, and photodynamic therapy—can address the inherent shortcomings of traditional oral cancer treatment modalities, such as surgery, radiation therapy, and chemotherapy, from different perspectives. Traditional regimens are often accompanied by practical issues such as tissue damage and adverse reactions, whereas the aforementioned emerging therapies each possess distinct mechanisms of action. When these different treatment modalities are combined and used in conjunction, they can exert a synergistic antitumor effect, offering potential value in optimizing treatment outcomes for patients and reducing the incidence of various treatment-related complications. However, objectively speaking, the research evidence supporting these therapies still has significant limitations. Most studies remain at the *in vitro* cellular level, and the clinical trials that have been conducted generally have small sample sizes and relatively limited follow-up periods. Although existing trial data confirm that these treatment modalities possess considerable antitumor activity, there remains substantial room for further research and refinement regarding the specific mechanisms of action and appropriate clinical applications of each therapy.

3. Conclusions

Surgery, radiation therapy, and chemotherapy are currently the primary clinical treatment options for oral cancer; however, these interventions often impair the physiological functions of the oromandibular system, alter facial appearance, and cause various treatment-related adverse effects, and patients' long-term survival outcomes still need improvement. This article reviews four emerging treatment strategies for oral cancer—non-anticoagulant heparin derivatives, molecularly targeted therapy, photothermal therapy, and photodynamic therapy—each of which demonstrates unique clinical value. Non-anticoagulant heparin derivatives can inhibit tumor cell proliferation, migration, and invasion, exhibit minimal cytotoxicity toward normal oral cells, and are well-suited for combination with traditional chemotherapy drugs; molecularly targeted therapy can specifically block tumor-driving signaling pathways, mediate cancer cell apoptosis, and induce cell cycle arrest; photothermal and photodynamic therapies rely on light-responsive agents to destroy tumors, and when used in combination with radiotherapy and chemotherapy, they can exert synergistic antitumor effects while preserving surrounding normal tissues as much as possible.

At this stage, most of the relevant research data comes from *in vitro* cell experiments, and clinical

studies have primarily involved small sample sizes and short-term observations. Key issues—such as drug safety risks, optimal dosing strategies, standardized protocols for combination therapy, and long-term patient prognosis—have not yet been fully addressed. Large-scale animal studies and long-term clinical follow-up studies are still needed to provide a basis for the practical application and translation of these technologies. Overall, these emerging therapies can serve as a valuable supplement to the traditional oral cancer treatment system. Future research should focus on improving drug formulations, identifying more scientifically sound combination therapy regimens, and accelerating the transition of basic research findings into clinical practice. The goal is to maximize the preservation of patients' oral physiological functions and improve their long-term quality of life while effectively controlling tumor progression.

Acknowledgement

Funding: University-level Research Project of Jingchu University of Technology (ZKQN2503)

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